Alzheimer's Agents

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Dementia Type		
		AD – mild to moderate	AD – moderate to severe	PD – mild to moderate
Acetylcholinesterase Inhibitors (AChEIs)				
donepezil (Aricept®, Aricept® ODT)[1,2]	generic/Eisai	X	X	--
galantamine (Razadyne®, Razadyne ER®, Razadyne® Oral Solution)[3,4]	generic/Janssen Pharmaceuticals	X	--	--
rivastigmine (Exelon®, Exelon® Oral Solution)[5,6]	generic/Novartis	X	--	X
rivastigmine (Exelon® Patch)[7]	Novartis	X	X	X
(N-methyl-D-aspartate) NMDA receptor antagonist				
memantine (Namenda®, Namenda® Oral Solution, Namenda XR)[8,9]	Forest	--	X	--

AD - Alzheimer's disease

PD – Parkinson's disease

OVERVIEW

Dementia is characterized by irreversible loss of or decline in memory and other cognitive abilities. Alzheimer's disease (AD) is the most common type of dementia, accounting for 60 to 80 percent of dementia disorders in the elderly and is the sixth leading cause of death in the United States.[10,11,12,13] Other types of dementia include dementia with Lewy bodies, vascular dementia, mixed dementia, and frontotemporal dementia. Dementia may also be associated with Human Immunodeficiency Virus (HIV), Huntington's disease, Korsakoff's syndrome, Multiple Sclerosis (MS), Parkinson's disease (PD), and Creutzfeldt-Jakob disease. Many other conditions can cause dementia symptoms, such as thyroid disorder and vitamin deficiencies, but are reversible once the underlying condition is addressed.

AD is characterized by progressive cognitive decline associated with impairment of activities of daily living (ADL) and behavioral disturbances. Patients with AD eventually lose all cognitive, analytical, and physical functioning. Ten warning signs of AD include memory loss that disrupts daily life, challenges in planning or solving problems, difficulty completing familiar tasks, confusion with time or place, trouble understanding visual images and spatial relationships, difficulties with speaking or writing, misplacement of items, decreased or poor judgment, withdrawal from work or social activities, and mood or personality changes. In addition, there are seven stages of AD over the course of the disease and individuals will not experience the same symptoms or rate of disease progression.

General agreement among AD researchers includes identified risk factors that increase the risk of being diagnosed with AD. These risk factors include age > 65 years old and the risk doubles every five years after the age of 65 until the age of 85 when the risk reaches nearly 50 percent. Family history also plays a part when the patient has a parent, sibling, or child with Alzheimer's and will be more likely to develop the disease. As a result, genetics play a role with AD in both risk genes and deterministic genes. Approximately 20 to 25 percent of patients with AD have the gene apolipoprotein E-e4 (APOE-e4), while those with deterministic genes (precursor protein (APP), presenilin-a (PS-1), and presenilin-2 (PS-2) are guaranteed to have the disease. Genetic testing is available for these biomarkers but health professionals do not recommend routine genetic testing for screening or diagnosis; instead, diagnosis is based on a complete medical assessment including mental status testing, physical, neurological, and blood tests to rule out other causes.[14]

Although the causes of AD have not been completely identified, the etiology of the disease is thought to be multifactorial. The features of AD with much tighter correlation among clinical symptoms is between neurofibrillary pathology and cognitive impairment and the aspect more coupled with cognitive impairment is neuro-degeneration, particularly synapse loss. As AD progresses, the discovery of extensive cholinergic cell loss led to the cholinergic hypothesis and the development of drugs that target the cholinergic system. The cholinergic hypothesis suggests that a dysfunction of acetylcholine (ACh)-containing neurons in the brain plays a part in the decline of cognitive function seen in patients with AD.[15]

Abnormalities also exist in the glutamate pathways of patients with AD. Glutamate is the main excitatory neurotransmitter in the cerebral cortex and hippocampus. The glutamate-gated N-methyl-D-aspartate (NMDA) receptor is activated during memory formation. Persistent activation of NMDA receptors due to chronic, excessive glutamate release is toxic to neurons, and the over activation leads to deficits in cognitive function and neuronal death.[16] Loss of these glutamatergic fibers correlates with the clinical signs of dementia.[17,18]

Some evidence indicates that a compromise of the serotonergic system contributes significantly to the onset and progression of AD. Specifically, data suggest that serotonin receptors modulate ACh, as well as other neurotransmitters, including glutamate, dopamine, and norepinephrine.[19,20] Regardless of the specific cause, the characteristic features of tangle pathology and neuronal death are noted in all cases.

Tacrine (Cognex) was the first cholinesterase inhibitor approved; however, this agent is no longer available in the U.S. market as newer acetylcholinesterase agents with less adverse effects are available. Three acetylcholinesterase inhibitors (AChEIs) commonly utilized for the treatment of AD are galantamine (Razadyne, Razadyne ER), rivastigmine (Exelon, Exelon Patch), and donepezil (Aricept, Aricept ODT). Each of these drugs has shown cognitive benefit over placebo; however, it remains unclear if their use slows disease progression, cognitive decline, delays placement in nursing homes, or alters mortality.

Parkinson's disease (PD) is a fairly common neurological disorder that affects two percent of adults older than 65 years old. The National Parkinson's Foundation estimates that 50 to 80 percent of those with PD will eventually experience PD dementia and the average time from onset of PD to developing dementia is about 10 years. For dementia related to PD, the dementia symptoms progress similar to dementia with Lewy bodies or Alzheimers. Early onset Parkinson's disease primarily targets movement

but, as the disease progresses, mental functions including memory and task completion are impacted. Brain changes include deposits of alpha-synuclein clumps (Lewy bodies) in the substantia nigra which is thought to cause degeneration of the dopamine-producing nerve cells. In addition, patients with dementia with PD or dementia with Lewy bodies have plaques and tangles. Plaques and tangles are also hallmark indicators of Alzheimers disease (AD).[21, 22]

Memantine (Namenda, Namenda XR), a NMDA receptor antagonist, has been shown to improve cognition in moderate to severe dementia and is FDA-approved for treatment of moderate to severe AD.[23,24] Due to conflicting data on the efficacy of memantine in mild AD, the FDA rejected a request to approve memantine for mild AD.[25] There are data showing that using memantine in combination with AChEIs is beneficial in moderate to severe AD patients.[26,27,28]

Patients should be evaluated every six months by MMSE score and global, functional, and behavioral assessment if they are being treated with any of these medications. Caregiver's input on the patient's condition at follow-up should be obtained. Medication should only be continued if it is determined that it is producing a beneficial effect. There are limited data showing evidence for a prolonged duration of effect.[29,30,31,32,33]

In 2011, National Institute for Aging (NIA) and the Alzheimer's Association updated proposed criteria and guidelines by expanding the definition of Alzheimer's to include two new phases of the disease: presymptomatic and mildly symptomatic but pre-dementia, along with dementia caused by Alzheimer's.[34,35,36] This reflects current thinking that Alzheimer's begins creating distinct and measurable changes in the brains of affected people years, perhaps decades, before memory and thinking symptoms become noticeable.[37]

Management objectives for treatment of AD include improving cognition and delaying disease progression, as well as promoting quality of life and social functioning, treating with dignity, educating and supporting caregivers, and assisting with decision-making and competency determinations. In 2008, the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) developed guidelines for the pharmacological treatment of dementia.[38] The AAFP-ACP guideline panel reviewed the medical literature and found limited evidence regarding the effectiveness of the approved drugs in regard to these outcomes: cognition, global function, behavior/mood, and quality of life/activities of daily living. The guidelines recommend that the decision to initiate a trial of therapy with an AChEI or memantine should be based on individual assessment by a clinician. Tolerability, adverse effect profile, ease of use, and cost should be considered when selecting treatment. Finally, the guidelines indicated that there is an urgent need for further research on the clinical effectiveness of the current pharmacologic management of dementia.

Dementia associated with PD is similar in nature to AD in that, in most cases, amyloid plaques and neurofibrillary tangles are present.[39] In dementia associated with PD, cholinergic deficits are the most consistent findings associated with cognitive and neuropsychiatric symptoms.[40,41,42,43] Rivastigmine (Exelon, Exelon Patch) is FDA-approved for mild to moderate dementia associated with Parkinson's disease.

PHARMACOLOGY

Acetylcholinesterase Inhibitors (AChEIs)

AChEIs exert their therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of ACh through reversible inhibition of its hydrolysis by acetylcholinesterase (AChE). Centrally, the resulting increase in ACh improves cognition. Peripheral enhancement of ACh causes the gastrointestinal adverse effects noted with AChEIs. As the disease progresses, the therapeutic effect of the AChEIs may lessen as fewer cholinergic neurons remain functionally intact.[44] Rivastigmine is also a selective inhibitor of butyrylcholinesterase (BuChE).

NMDA receptor antagonist

Memantine (Namenda, Namenda XR) is a low to moderate affinity, uncompetitive NMDA receptor antagonist that binds preferentially to NMDA receptor-operated cation channels. Memantine allows the NMDA receptor to be activated during physiological memory formation but blocks the receptor during pathological (excitotoxic) activation.[45,46] Memantine also demonstrates antagonistic effects at the serotonin and nicotinic receptors.[47,48]

PHARMACOKINETICS

Drug	Half-Life (hr)	Metabolism	Protein Binding (%)
Acetylcholinesterase Inhibitors (AChEIs)			
donepezil (Aricept, Aricept ODT)[49,50]	70	CYP2D6, 3A4	96
galantamine (Razadyne, Razadyne ER)[51,52]	7	CYP2D6, 3A4	18
rivastigmine (Exelon, Exelon Patch)[53]	1.5 (oral) 3 (patch)	hydrolysis by esterases	40
NMDA receptor antagonist			
memantine (Namenda, Namenda XR)[54,55]	60-80	renal tubular secretion and partial hepatic metabolism	45

CONTRAINDICATIONS/WARNINGS[56,57,58,59,60,61,62]

Cholinesterase inhibitors (donepezil [Aricept, Aricept ODT], galantamine [Razadyne, Razadyne ER], rivastigmine [Exelon, Exelon Patch] and NMDA receptor antagonists memantine (Namenda, Namenda XR) are contraindicated for patients with known hypersensitivity to the ingredients or any excipients. Rivastigmine patch is contraindicated in previous history of application site reactions with rivastigmine transdermal patch suggestive of allergic contact dermatitis. Rivastigmine is also contraindicated in previous history of application site reactions with rivastigmine transdermal patch suggestive of allergic contact dermatitis, in the absence of negative allergy testing.

Cholinesterase inhibitors are likely to exaggerate succinylcholine-type and other similar neuromuscular agents during anesthesia, potentially resulting in prolonged neuromuscular blockade and extended

respiratory depression; may increase gastric acid secretion due to increased cholinergic activity and should be monitored closely for symptoms of active or occult gastrointestinal bleeding.

In addition, cholinesterase inhibitors may have vagotonic effects that may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported with the use of donepezil and rivastigmine. In randomized controlled trials, bradycardia was reported more often with galantamine patients than with those receiving placebo; however, the bradycardia was rarely severe and rarely required treatment discontinuation.

Cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease due to their cholinomimetic effects.

Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of AD. In clinical trials seizures occurred in 0.3 percent of patients treated with memantine and 0.6 percent of patients treated with placebo.

Drugs that increase cholinergic activity (rivastigmine, donepezil, and galantamine) may cause urinary obstruction. Conditions that raise urine pH may decrease urinary elimination of memantine resulting in increased plasma concentrations.

Patients prescribed oral or transdermal rivastigmine at higher than the recommended dose have experienced significant gastrointestinal adverse effects, including nausea, anorexia/decreased appetite, and weight loss. When starting on therapy, the patient should be started at the lowest dose and then titrated to the maintenance dose. If treatment is interrupted for longer than seven days, treatment should be reinitiated with the lowest dose.

Medication errors have been known to occur with rivastigmine (Exelon) transdermal and have resulted in serious adverse events; some cases have required hospitalization, and rarely, led to death. The majority of medication errors have involved not removing the old patch when putting on a new one and the use of multiple patches at one time. Patients and caregivers must be given proper instruction on the dosage and administration of rivastigmine patches and patches should be removed after 24 hours.

Disseminated hypersensitivity reactions of the skin have been reported with the use of rivastigmine with both the oral and transdermal routes of administration. Treatment should be discontinued if disseminated hypersensitivity reaction of the skin occurs. Application site reactions may occur with rivastigmine patch. Discontinue treatment if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g., increasing erythema, edema, papules, vesicles), and if symptoms do not significantly improve within 48 hours after removal of patch. Patients who continue to require rivastigmine therapy should be switched to oral therapy only after negative allergy testing.

DRUG INTERACTIONS[63,64,65,66,67,68,69]

Antimuscarinics are functional antagonists of the AChEIs and reduce the effectiveness of AChEIs when coadministered.[70,71] Drugs with anticholinergic effects have been shown to interfere with the activity of the AChEIs. Common anticholinergics include amantadine, cyclobenzaprine, orphenadrine, disopyramide, and sedating antihistamines.

Parasympathomimetic drugs can produce additive pharmacologic effects when used with AChEIs. Concurrent use is unlikely to be tolerated and should be avoided. Additionally, a synergistic effect would be expected when cholinesterase inhibitor is given concurrently with succinylcholine or similar neuromuscular blocking agents.

Donepezil (Aricept, Aricept ODT) is metabolized by CYP2D6 and 3A4; therefore, there is potential for an interaction with drugs that are inhibited or metabolized by these isoenzymes. Although clinically significant interactions have not been documented, patients taking drugs that are metabolized by the same isoenzymes should be monitored. Donepezil is highly protein bound (96 percent), but interactions where donepezil displaces or is displaced by other protein bound drugs have not been reported.

Rivastigmine (Exelon, Exelon Patch) is hydrolyzed by esterases, but no significant drug interactions have been reported.

Galantamine (Razadyne, Razadyne ER) is a primary substrate for CYP3A4 and is metabolized to a lesser extent by CYP2D6. Coadministration of galantamine with a strong inhibitor of CYP3A4, such as ketoconazole, increased the area under the curve (AUC) of galantamine by 30 percent. When administered with the strong inhibitor of CYP2D6, paroxetine 20 mg per day, the oral bioavailability of galantamine increased by about 40 percent. Galantamine has not been shown to have a significant effect on other drugs metabolized by the CYP450 enzyme system.[72]

The use of memantine (Namenda, Namenda XR) in combination with other NMDA antagonists, such as amantadine, ketamine, and dextromethorphan, has not been evaluated and use should be approached with caution. Memantine is partially excreted by renal tubular secretion.[73] Coadministration of memantine with other drugs that are excreted in this manner, such as hydrochlorothiazide, nicotine, and ranitidine, may result in increased serum concentrations of one or both drugs. When given with metformin, competition between the two drugs for renal elimination may increase the risk of lactic acidosis due to accumulation of metformin. Conditions that raise urine pH may decrease urinary elimination of memantine resulting in increased plasma levels.

ADVERSE EFFECTS

Drug	Nausea	Vomiting	Anorexia	Diarrhea	Dizziness	Headache	Withdrawal due to Adverse Event
Acetylcholinesterase Inhibitors (AChEIs)							
donepezil (Aricept, Aricept ODT)[74] mild-mod AD	11 (6)	5 (3)	4 (2)	10 (5)	8 (6)	10 (9)	5-13 (5)
donepezil (Aricept, Aricept ODT)[75] severe AD	6 (2)	8 (4)	8 (4)	10 (4)	2 (1)	4 (3)	12 (7)
galantamine (Razadyne)[76]	24 (9)	13 (4)	9 (3)	9 (7)	9 (6)	8 (5)	7-10 (7)
galantamine ER (Razadyne ER)*[77]	nr	nr	nr	nr	nr	nr	nr
rivastigmine (Exelon)[78] mild-mod AD	47 (12)	31 (6)	17 (3)	19 (11)	21 (11)	17 (12)	6-15 (4-5)
rivastigmine (Exelon Patch)[79] mild-mod AD	7-21 (5)	6-19 (3)	3-9 (2)	6-10 (3)	2-7 (1)	3-4 (2)	8.6-9.6 (5)
rivastigmine (Exelon Patch)[80] severe AD Exelon 13.3 mg/24 h (4.6 mg/24 h)	6 (3)	7 (3)	7 (3)	7 (5)	nr**	nr**	20.5 (14.2)
NMDA receptor antagonist							
memantine (Namenda)[81]	reported	3 (2)	reported	reported	7 (5)	6 (3)	no difference from placebo
memantine ER (Namenda XR)[82]	reported	2 (1)	reported	5 (4)	5 (1)	6 (5)	10 (6.3)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

*In clinical trials, once daily treatment with Razadyne ER was well tolerated and adverse events were similar to those seen with Razadyne.

**Dizziness and headache are adverse events of rivastigmine patch, although not specifically reported in severe AD study

In general, a dose-response relationship exists for the incidence of adverse events for the agents in this class.

In severe AD patients taking rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h, agitation (12 versus 14 percent), urinary tract infections (eight versus 10 percent), fall (eight versus six percent), and insomnia (seven versus four percent) have been reported. Application site reactions have been reported for rivastigmine patch.

SPECIAL POPULATIONS[83,84,85,86,87,88,89,90]

Pediatrics

There are no adequate and well-controlled trials documenting the safety and efficacy of the AChEIs in any illness occurring in children; therefore, the AChEIs are not recommended for use in children. Also, there are no well-controlled trials demonstrating safety and efficacy for the NMDA receptor agonist, memantine, in children.

Pregnancy

Donepezil is classified as Pregnancy Category C. Galantamine, rivastigmine, and memantine are classified as Pregnancy Category B.

Renal Impairment

The dose of galantamine should be titrated cautiously in patients with moderate renal impairment, and galantamine and the total daily dose generally should not exceed 16 mg/day. The use of galantamine is not recommended in patients with severe renal impairment (CrCL <9 mL/min). Pharmacokinetic studies have shown that clearance of oral rivastigmine is reduced in patients with moderate to severe renal impairment (CrCL <50 mL/min); therefore, total daily doses of oral rivastigmine may need to be reduced. In patients with severe renal impairment (CrCL 5 to 29 mL/min), the target dose of memantine immediate-release tablets is 5 mg twice a day and for memantine extended-release capsules is 14 mg daily.

Hepatic Impairment

The total daily dose of galantamine in patients with moderate hepatic impairment (Child-Pugh score 7 to 9) should not exceed 16 mg/day, and galantamine use is not recommended in patients with severe hepatic impairment (Child-Pugh score 10 to 15). Memantine should be used with caution in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment (Child-Pugh score 5-9), rivastigmine oral and patches total daily dose should be reduced. In the patches, the initial and maximum dose should remain at 4.6 mg/24 hours.

DOSAGES[91,92,93,94,95,96,97,98]

Drug	Starting Dosage	Minimum Therapeutic Dosage* (minimum time to reach)	Target Dosage** (minimum time to reach)	Special Considerations	Dosage Forms
Acetylcholinesterase Inhibitors (AChEIs)					
donepezil (Aricept, Aricept ODT)	5 mg daily	5 mg daily (0 weeks)	10 mg daily (4-6 weeks) 23 mg (3 months)	--	tablets: 5, 10, 23 mg tablets, orally disintegrating: 5, 10 mg
galantamine (Razadyne)	4 mg twice daily	8 mg twice daily (4 weeks)	12 mg twice daily (8 weeks)	moderate hepatic and/or renal impairment – reduce target Dosage	generic tablets: 4, 8, 12 mg Razadyne oral solution: 4 mg/mL
galantamine ER (Razadyne ER)	8 mg daily	16 mg daily (4 weeks)	24 mg daily (8 weeks)	moderate hepatic and/or renal impairment – reduce target Dosage	generic capsules: 8, 16, 24 mg
rivastigmine (Exelon)	1.5 mg twice daily	3 mg twice daily (2 weeks)	6 mg twice daily (6 weeks)	moderate to severe renal and/or mild to moderate hepatic impairment or low (<50 kg) body weight reduce target dose	capsules: 1.5, 3, 4.5, 6 mg oral solution: 2 mg/mL
rivastigmine (Exelon Patch)	4.6 mg/24 hours	9.5 mg/24 hours (4 weeks)	9.5 mg/24 hours (4 weeks); for severe AD after a minimum additional four weeks, may increase to 13.3 mg/24 hours (max dose)	mild to moderate hepatic impairment or low (<50 kg) body weight reduce target dose	transdermal system: 4.6 mg/24 hours ($5\ cm^2$ size contains 9 mg drug) 9.5 mg/24 hours ($10\ cm^2$ size contains 18 mg drug) 13.3 mg/24 hours ($15\ cm^2$ contains 27 mg drug)

Dosages (continued)

Drug	Starting Dosage	Minimum Therapeutic Dosage* (minimum time to reach)	Target Dosage** (minimum time to reach)	Special Considerations	Dosage Forms
NMDA receptor antagonist					
memantine (Namenda)	5 mg daily	nd	10 mg twice daily (3 weeks)	moderate renal impairment – consider dosage reduction	tablets: 5, 10 mg oral solution: 2 mg/mL
memantine ER (Namenda XR)†	7 mg daily	nd	28 mg once daily (4 weeks)	severe renal impairment – 14 mg once daily	extended release capsules: 7, 14, 21, 28 mg

nd = data not available

* Minimum Therapeutic Dosage – the lowest dosage at which a statistically significant improvement in cognition over placebo has been observed.

** Target Dosage – Recommended dosage in the prescribing information.

† Patients on Namenda 10 mg or lower may be switched to Namenda XR 28 mg following the final tablet dose

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant of clinical trials; however, there are no randomized, double-blind, directly comparative studies of the drugs in this class. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance and use data analysis techniques consistent with the study question. Due to the paucity of high-quality, active-control, randomized, controlled trials, placebo-controlled studies of these drugs in dementia associated with AD and PD were included in the review. Studies were included if they were of six months (24 weeks) duration or greater and had recognized cognitive and/or functional primary outcome measures. Due to high rates of loss to follow-up in many studies of the drugs in this class, clinical trials with less than 50 percent loss to follow-up were considered in this review. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Efficacy Scales

Various validated assessment scales are used to evaluate patient response and efficacy in clinical trials for drugs used in the treatment of dementia associated with AD and PD.

Cognition

Alzheimer's Disease Assessment Scale (ADAS) – This is a standardized assessment of cognitive function. A trained observer evaluates memory, language, and praxis. This scale is the gold standard for measuring change in cognitive function in drug trials.[99] The FDA has proposed that therapeutic response to drugs used for AD be defined as an improvement of four or more points on the ADAS.[100]

Behavioral Rating Scale for Geriatric Patients (BGP) – This measures observable aspects of cognition, function, and behavior. The total BGP score has a significant association with the level of dependency.[101]

Mini-Mental Status Examination (MMSE) – This is the most widely used measure of cognitive function. It assesses orientation, registration, attention, recall, and language.[102] The MMSE has been shown to successfully differentiate dementia, depression, or a combination of the two.[103]

Severe Impairment Battery (SIB) - This is a cognitive assessment tool that examines elements of attention, orientation, language, memory, visual-spatial ability, construction, praxis, and social interaction.[104]

Global / Functional

Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL) - The ADCS-ADL consists of questions directed at the patient's caregiver and is used to measure the functional capacity of the patient.[105] A subset of 19 items rates the patient's ability to eat, dress, bathe, telephone, travel, shop, and perform other household chores.[106] A modification of this assessment, ADCS-ADL-sev, is used for patients with severe dementia.

Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) – The ADCS-CGIC is a seven point categorical scale that provides a single global rating of change from baseline ranging from marked improvement to no change to marked worsening. The ADCS-CGIC is a valid and reliable instrument for use in clinical trials.[107]

Bristol Activities of Daily Living scale (BrADL) - This scale, which assesses 20 daily living abilities, was designed specifically for use in patients with dementia. The validity of this scale was measured by verifying that the items in the scale were important to caregivers and that there is good test-retest reliability.[108]

Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-plus) - There are a variety of CIBIC formats each different in depth and structure. The CIBIC-plus requires use of caregiver information. Generally, CIBIC results are not comparable across trials.[109]

Disability Assessment for Dementia scale (DAD) - This is a newer functional scale, rated by a trained observer, specifically developed for patients with AD. This scale assesses basic and instrumental ADLs.[110]

Neuropsychiatric Inventory (NPI) - This is a validated instrument that measures disturbed behavior through assessment of ten domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, and aberrant motor behavior.[111] In the NPI, each item is rated according to its frequency and severity based on a caregiver interview.

Progressive Deterioration Scale (PDS) – This measures function in both instrumental and basic ADLs by asking the caregiver to assess function using 27 items and to rate the patient's performance on a visual analogue scale that employs a fulcrum line with bipolar descriptions of ADLs at either end. This scale has been shown to be reliable and valid.[112]

Mild to Moderate Dementia of the Alzheimer's Type

donepezil (Aricept) and placebo

In a double-blind study, 473 patients with mild to moderate AD were randomized to receive 24 weeks of donepezil 5 mg/day, donepezil 10 mg/day, or placebo, followed by a six-week single-blind washout period.[113] Cognitive function, as measured by the ADAS-cog, deteriorated significantly less in the active treatment groups compared to placebo ($p<0.0001$) at weeks 12, 18, and 24. The CIBIC-plus ($p<0.005$) and MMSE ($p<0.001$) scores also were better in both donepezil groups relative to placebo. At the end of the six-week placebo washout phase, ADAS-cog scores and CIBIC plus ratings were not significantly different for the three groups. Cholinergic adverse effects (primarily diarrhea, nausea, and vomiting) were reported more often in the 10-mg/day group than either the 5-mg/day or placebo groups.

Adverse effects were transient and generally mild in severity. There was a 22 percent loss to follow-up in the study.

Two hundred and seven patients with moderate AD were randomized to donepezil (5 mg/day for four weeks with titration to 10 mg/day based on physician judgment) or placebo for 24 weeks.[114] The double-blind study was completed by over 80 percent of patients in each treatment group. The primary outcome measure, CIBIC-plus, significantly favored active treatment over placebo at week 24 ($p=0.0003$). The 24-week response rate was 70 percent in the donepezil group and 47 percent in the placebo group ($p=0.0007$). Both the MMSE and SIB showed improvement in the active treatment group ($p=0.0002$ and $p=0.0026$, respectively) compared to placebo at 24 weeks. Disability Assessment for Dementia remained at or above baseline levels throughout the study for the donepezil group, while the placebo group showed a steady decline; treatment differences were significant at week 24 ($p<0.0001$). The NPI showed benefit with donepezil treatment with significant differences with placebo in delusions ($p=0.0073$), apathy ($p=0.0131$), and aberrant motor behavior ($p=0.0232$). A similar percentage of patients in the active and placebo groups (82 and 80 percent, respectively) experienced adverse effects.

In a double-blind study, 565 patients with mild to moderate AD were randomized to donepezil 5 mg/day or placebo.[115] A 12-week run-in period was completed by 486 patients, who were then re-randomized to either donepezil 5 or 10 mg/day or placebo, with treatment continuing as long as deemed appropriate. Over the first two years of the study, cognition (measured by MMSE) and functionality (measured by BADLS) among patients in the active treatment groups were significantly better than in the placebo group ($p<0.001$ for both comparisons). At three years, there was no significant benefit with donepezil compared to placebo in rates of institutionalization (42 versus 44 percent, $p=0.4$). There was no difference between groups in the progression of disability (measured by BADLS) or in behavioral and psychological symptoms (measured by NPI).

donepezil (Aricept) and galantamine (Razadyne)

In a multicenter, rater-blinded study, 182 patients with AD were randomized to 52 weeks of treatment with galantamine (8 mg/day for four weeks, then 16 mg/day for four weeks with optional titration to 24 mg/day) or donepezil (5 mg/day for four weeks with optional titration to10 mg/day).[116] The study was completed by 78 to 80 percent of patients in each group. At the end of the study, approximately 70 percent of patients in each group were receiving the maximum dose. In each group, the BrADL scores were constant through month nine, then worsened thereafter. At week 52, there was a similar functional responder rate (defined as no increase in BrADL score), 39 percent, in each group. In terms of cognition, galantamine patients' scores on the MMSE at week 52 did not differ significantly from baseline (-0.52 ± 0.39, $p<0.5$ versus baseline), whereas donepezil patients' scores deteriorated significantly from baseline (-1.58 ± 0.42, $p<0.0005$ versus baseline). The between-group difference in MMSE change did not reach statistical significance ($p\leq0.1$). The ADAS-cog responder rates were not statistically different in the galantamine (45 percent) and donepezil (32 percent; $p<0.1$) groups at the conclusion of the study. Patients treated with galantamine who had MMSE scores of 12-18 demonstrated an increase (worsening) in the ADAS-cog/11 score of 1.61 ± 0.80 versus baseline, compared with an increase of 4.08 ± 0.84 for patients treated with donepezil. Additionally, caregivers of patients receiving galantamine were more likely to report reductions in burden compared with caregivers of patients receiving donepezil. Changes from baseline in NPI were similar for both treatment groups. Both galantamine and donepezil were well tolerated, with most adverse events

being transient, of mild to moderate intensity, and consistent with the findings of previous clinical trials.

galantamine (Razadyne) and placebo

A total of 636 patients with mild to moderate AD were evaluated in a six-month, double-blind trial.[117] Patients were randomized to galantamine at a target dose of either 24 or 32 mg/day or to placebo. Patients randomized to galantamine started therapy with 8 mg/day for the first week. The dose was increased weekly by 8 mg/day until patients were at their target dose of 24 or 32 mg/day which they continued for an additional five months. After a total of six months of treatment, patients receiving either dose of galantamine had significant improvement compared to placebo in ADAS-cog score ($p<0.001$ for both galantamine groups) and CIBIC-plus ($p<0.05$ for both galantamine groups). There was no significant difference between the galantamine groups. The loss to follow-up rate in the galantamine groups (32 to 42 percent) was higher than in the placebo group (19 percent). Of 438 patients completing the first phase of the study, 353 entered an open-label phase in which all patients received galantamine 24 mg/day after retitration. Mean ADAS-cog and DAD scores were unchanged from baseline in patients who received galantamine 24 mg/day for the entire 12-month period.

Patients completing two double-blind, placebo-controlled trials (n=699) were escalated to a 24 mg dose (12 mg twice daily) of galantamine during a period of two weeks and treated for 12 months beyond the initial 6.5-month, double-blind period (total treatment duration: 18.5 months).[118] The primary efficacy measure was the change from baseline in the ADAS-cog score at the conclusion of the study. Patients were maintained close to baseline cognitive ability for 12 months.

In a double-blind, parallel-group study, 653 patients with mild to moderate AD were randomized to receive galantamine titrated to 24 mg/day, galantamine titrated to 32 mg/day, or placebo.[119] The six-month study was completed by 525 (80 percent) of the enrollees. At the conclusion of the study, patients receiving either dose of galantamine had significantly better outcomes as measured by the ADAS-cog, ADCS-ADL, and CIBIC-plus ($p<0.05$ for all comparisons to placebo). The galantamine 32 mg/day dosage ($p<0.05$), but not the lower dose ($p=0.1$), was significantly better than placebo in blunting the progression of dementia as measured by DAD.

galantamine (Razadyne) and galantamine ER (Razadyne ER)

In a double-blind, parallel-group trial, 971 patients with mild to moderate AD were randomized to treatment for six months with galantamine 8 or 12 mg twice daily, galantamine ER 16 or 24 mg once daily, or placebo.[120] The mean change from baseline in ADAS-cog was similar in the galantamine (-1.6 ± 0.4) and galantamine ER (-1.3 ± 0.3) groups, and both treatments were superior to placebo (+1.3 ± 0.3). Compared to placebo, both galantamine regimens were associated with a significant improvement in ADCS-ADL but not in CIBIC-plus or NPI. Galantamine ER had similar tolerability and safety profiles compared with twice-daily galantamine.

rivastigmine (Exelon) and placebo

In a double-blind study, 725 patients with mild to moderately severe AD were randomized to receive either placebo or rivastigmine 1 to 4 mg/day (low dose) or 6 to 12 mg/day (high dose).[121] Doses were titrated up within the assigned dosage range over the first 12 weeks then continued at that dose for an additional 14 weeks. Patients in the high-dose rivastigmine group demonstrated improvement in the ADAS ($p<0.05$) and CIBIC-plus ($p<0.001$) compared to patients in the placebo group. The CIBIC-plus

improved more frequently in the high-dose rivastigmine group (37 percent) than in the low-dose (30 percent) or placebo (20 percent) groups.

rivastigmine patch (Exelon Patch) versus rivastigmine capsule (Exelon) and placebo

The efficacy, safety, and tolerability of rivastigmine transdermal patches were compared to rivastigmine capsules and placebo in the 24-week, double-blind, double-dummy, placebo- and active-controlled IDEAL (Investigation of transdermal Exelon in Alzheimer's disease) study with 1,195 participants with AD.[122] Patients were randomized to placebo or one of three active treatment target groups: 10-cm^2 rivastigmine patch (delivering 9.5 mg/24 hours – low dose group); 20-cm^2 rivastigmine patch (delivering 17.4 mg/24 hours – high dose group) or 6 mg rivastigmine capsule administered twice daily. Primary efficacy measures were ADAS-cog and Alzheimer's Disease Cooperative Study-Clinical Global and Impression of Change. Secondary outcome measures assessed a range of domains, including behavior, cognitive performance, attention, executive functions, and activities of daily living. All rivastigmine treatment groups showed significant improvement relative to placebo. The low dose patch group showed similar efficacy to capsules with approximately two-thirds fewer reports of nausea and vomiting; incidences were not statistically significantly different from placebo. The high dose patch group showed earlier improvement and numerically superior cognitive scores versus the low dose patch group with similar tolerability to capsules. Local skin tolerability was good.

A prospective outcome of the IDEAL study was to evaluate caregiver preference for rivastigmine patches compared to capsules.[123] Caregivers rated patch adhesion throughout. The AD Caregiver Preference Questionnaire (ADCPQ) assessed patch versus capsule from caregivers' perspective based on expectations, preferences, and satisfaction with treatment. A total of 1,059 caregivers completed the ADCPQ while their respective patients were on study drug. More than 70 percent of caregivers preferred the patch to capsules. It was preferred with respect to ease of use ($p<0.0001$) and ease of following treatment regimen ($p<0.0001$). Caregivers indicated greater satisfaction overall ($p<0.0001$) and less interference with daily life ($p<0.01$) with the patch versus capsule.

Moderate to Severe Dementia of the Alzheimer's Type

donepezil (Aricept) and placebo

Patients with moderate to severe AD were randomized to donepezil (5 mg/day for the first 28 days and 10 mg/day thereafter as per the clinician's judgment) or placebo in a 24-week, double-blind study.[124] The 290-patient study was completed by 84 to 86 percent of the patients in each group. Patients receiving donepezil showed benefits on the CIBIC-plus, the primary outcome measure, compared with placebo at all visits including week 24 ($p<0.001$). All other secondary measures including MMSE, SIB, DAD, and NPI showed significant differences between the groups in favor of donepezil at week 24. Adverse events were experienced by 83 percent of donepezil- and 80 percent of placebo-treated patients, the majority of which were rated mild in severity; eight percent of donepezil- and six percent of placebo-treated patients discontinued because of adverse effects.

Two hundred ninety patients with moderate to severe AD were randomized to receive donepezil (5 mg/day for four weeks, then 10 mg/day per clinician judgment) or placebo for 24 weeks.[125] In the double-blind study, the mean change from baseline in DAD, the primary endpoint, significantly favored donepezil over placebo ($p<0.0001$) at week 24. The specific components of DAD that favored donepezil were hygiene ($p<0.0001$), dressing ($p=0.0003$), and leisure/housework ($p=0.0037$).

Three hundred forty three patients with severe AD [MMSE scores one to 12 and Functional Assessment Staging (FAST) scores ≥ 6] were randomized to donepezil 10 mg daily (n=176) or placebo (n=167) for 24 weeks in a multinational, double-blind, placebo-controlled trial at 98 sites.[126] Donepezil was superior to placebo on SIB score change from baseline to endpoint (p=0.0001). Donepezil was favored at endpoint for CIBIC-plus and MMSE scores (p=0.0473 and p=0.0267). Donepezil was not significantly different from placebo on the ADCS-ADL-sev, NPI, CBQ (Caregiver Burden Questionnaire), or RUSP (Resource Utilization for Severe AD Patients). Adverse events reported were consistent with the known cholinergic effects of donepezil and its safety profile in patients with mild to moderate AD.

donepezil (Aricept) and rivastigmine (Exelon)

Patients with moderate to moderately severe AD were randomly assigned to rivastigmine 3 to 12 mg/day or donepezil 5 to 10 mg/day over a two-year period.[127] In the double-blind study, 994 patients received treatment, and 58 percent of these patients completed their assigned treatment regimen. The average decline in SIB, the primary efficacy measure, was similar between the two groups. Approximately 36 percent of patients in each group retained SIB scores that were equal or better than baseline. The two groups were also similar in the secondary measure of cognition, change in MMSE score from baseline, as well as in the change in NPI. At the conclusion of the study, 19 percent of patients receiving donepezil and 25 percent of those receiving rivastigmine retained ADCS-ADL scores that were equal or better than baseline (p=0.047). Fewer patients receiving donepezil (16 percent) than rivastigmine (26 percent) discontinued their assigned treatment due to adverse events. The most frequent reason for premature discontinuation in both treatment groups was adverse events, primarily gastrointestinal. Adverse events were more frequent in the rivastigmine group during the titration phase but similar in the maintenance phase.

***rivastigmine (Exelon Patch) 13.3 mg/24 h versus rivastigmine (Exelon Patch)* 4.6 mg/24 h**

A randomized, double-blind, parallel-group, prospective, 24-week multicenter study in patients with severe Alzheimer's disease, evaluated the efficacy and safety of rivastigmine 13.3 mg/24 h patch versus 4.6 mg/24 h patch.[128, 129] A total of 716 patients with a Mini-Mental Status Examination (MMSE) score of $\geq$3 to $\leq$ 12 were randomized into one of the following treatments: rivastigmine patch 13.3 mg/24 h (n=356) or rivastigmine patch 4.6 mg/24 h (n=360) in a 1:1 ratio. The study was divided into an 8-week titration phase followed by a 16-week maintenance phase. Participants with stable doses of memantine were allowed into the study. Primary outcomes were change from baseline at week 24 on the AD cooperative study-activities of Daily Living scale-severe impairment version (ADCS-ADL-SIV) and the Severe Impairment Battery (SIB) based on last observation carried forward (LOCF) approach. At the end of the study, the mean decline from baseline on assessments of cognition and overall function was significantly less with the 13.3 mg patch. Decline in the mean ADCS-ADL-SIV score from baseline for the MFAS-LOCF analysis was less at each time point in the 13.3 mg/24 hour (p=0.0247) rivastigmine patch treatment group than in the 4.6 mg/24 hours rivastigmine patch (p<0.001) treatment group. The 13.3 mg/24 h dose was statistically significantly superior to the 4.6 mg/24 h dose at weeks 16 and 24 (primary endpoint). The incidence of adverse events (AE) and serious adverse events (SAE) was comparable with the 13.3 and the 4.6/24 h patch (AE, 74.6 percent and 73.3 percent; SAE, 14.9 percent and 13.6 percent). Discontinuation due to AE and SAE was higher with the 13.3 than the 4.5 patch (AE, 13.5 percent and 10.9 percent; SAE 8.2 percent and 4.5 percent).

memantine (Namenda) and placebo

A total of 252 patients with moderate to severe AD were randomized to receive placebo or memantine titrated to 20 mg daily in double-blind fashion for 28 weeks.[130] Seventy-two percent of patients completed treatment. At endpoint (completion or early withdrawal from the study), patients receiving memantine had less deterioration on ADCS-ADL-sev (p=0.02), a primary efficacy variable, SIB (p<0.001) and FAST (p=0.02). There were no differences between active treatment and placebo in CIBIC-plus (p=0.06), MMSE (p=0.18), or NPI (p=0.03). Treatment with memantine did significantly reduce caregiver burden, as measured by BGP, in comparison to placebo (p=0.01). In an open-label, 24-week extension to the trial, 175 patients received memantine 20 mg daily.[131] In the study extension, subjects who had originally received placebo experienced a significantly slower rate of decline in ADCS-ADL-sev in the open-label phase compared to the randomized phase of the trial (p=0.21). Conversely, subjects who received memantine during all 52 weeks experienced a faster rate of decline in ADCS-ADL-sev in the open-label phase (p=0.035). The rate of decline in the CIBIC-plus slowed during the open-label phase in both original randomization groups compared to the randomized phase (p<0.001 for both groups). While participants who received memantine during the entire 52-week treatment period experienced a similar rate of decline in the SIB during the randomized and open-label study phases (p=0.086), the outcome improved during the open-label phase for those who had received placebo during the randomized phase (p=0.049).

In a 24-week, double-blind, placebo-controlled trial, patients not receiving a cholinesterase inhibitor (n=350) were randomized to receive memantine 20 mg/day or placebo.[132] Prospectively defined analyses failed to demonstrate a statistically significant benefit of memantine treatment compared with placebo on the SIB at the endpoint of 24 weeks although a significant advantage was observed at weeks 12 and 18. The 19-item ADCS-ADL did not differ significantly between groups in any analysis. CIBIC-plus did not significantly favor memantine at week 24 despite a significant advantage for memantine at weeks 12 and 18. Other secondary outcomes showed no significant treatment differences. Post-hoc analyses of potentially confounding covariates and alternative methods of imputing missing data did not substantially alter the results. Due to violations of normality assumptions for the SIB and ADCS-ADL19, nonparametric analyses were performed; statistically significant benefit of memantine over placebo was demonstrated at week 24 for the SIB but not the ADCS-ADL19. Type and incidence of adverse events were similar in both groups.

Data from six randomized, double-blind, placebo-controlled, six-month studies were pooled and a subgroup of patients (867 patients on placebo and 959 patients on memantine) with moderate to severe AD (MMSE < 20) was analyzed.[133] "Clinical worsening" was defined as a decline on the ADAS-cog or the SIB and on the CIBIC-plus and the ADCS-ADL and "marked clinical worsening" was defined as ≥ 4 points decline on the ADAS-cog or ≥5 points on the SIB and decline on the CIBIC-plus and the ADCS-ADL. More placebo-treated than memantine-treated patients showed any clinical worsening (28 versus 18 percent; p<0.001) and 21 percent placebo-treated patients compared to 11 percent memantine-treated patients had marked clinical worsening (p<0.001).

In a 24-week, double-blind study, 404 patients with moderate to severe AD and MMSE scores of 5 to 14 who were receiving stable doses of donepezil were randomized to memantine at a starting dose of 5 mg/day increased to 20 mg/day or placebo.[134] The change in total mean scores favored memantine versus placebo for both primary outcome measures, SIB (p<0.001), and ADCS-ADL (p=0.03). Secondary outcomes, including BGP (p=0.001) and NPI (p=0.002), also showed significant benefits of memantine compared to placebo. Improvement in CIBIC-plus occurred in 55 percent of memantine patients and 45

percent of those receiving placebo (p=0.03). Treatment discontinuations because of adverse events for memantine versus placebo were 15 (7.4 percent) versus 25 (12.4 percent), respectively.

memantine ER (Namenda XR) and placebo

Extended-release memantine was studied in a randomized, double-blind placebo controlled trial in 677 outpatients with moderate to severe Alzheimer's disease.[135,136] Patients were diagnosed with AD by DSM-IV criteria and NINCDS-ADRDA criteria with a Mini Mental State Examination (MMSE) score ≥ 3 and ≤ 14. All patients had been receiving acetylcholinesterase inhibitor (AChEI) therapy at a stable dose for three months prior to screening. The mean patient age was 76.5 years with a range of 49 to 97 years, and approximately 72 percent of patients were female and 94 percent were Caucasian. Patients were randomized to receive either extended-release memantine 28 mg/day or placebo while continuing to receive an AChEI (donepezil, galantamine, or rivastigmine). Co-primary efficacy parameters of Severe Impairment Battery (SIB) to assess cognitive performance, and the Clinician's Interview-Based Impression of Change (CIBIC-Plus) were used to assess efficacy every four weeks for 24 weeks. After 24 weeks, the mean difference in the SIB change scores for the memantine XR 28 mg/AChEI-treated (combination therapy) patients compared to the patients on placebo/AChEI (monotherapy) was 2.6 units (least squares mean difference [95 % CI] 2.6 [1.0, 4.2]; p=0.001), CIBIC-Plus (p=0.008), and verbal fluency test (p=0.004); Memantine ER 28 mg/AChEI treatment was statistically significantly superior to placebo/AChEI based on an LOCF analysis. Memantine ER did not achieve significance on the secondary endpoint of Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL19) (p=0.177). Adverse events with a frequency of five percent or greater than placebo that were more prevalent in the memantine group were headache and diarrhea.

donepezil (Aricept) 10 mg and 23 mg daily

A 24-week, randomized, double-blind trial evaluated continuation of 10 mg daily of donepezil versus increasing to 23 mg daily.[137] This study randomized 1,467 patients, aged 45 through 90 years, who were taking donepezil 10 mg daily for at least 12 weeks. The effectiveness analyses included 1,371 patients (mean age 73.8 years). A total of 296 (30.2 percent) patients withdrew from the donepezil 23 mg group, and 87 (17.9 percent) patients withdrew from the donepezil 10 mg group. After 24 weeks, the change in least squares mean changes from baseline (LSM [SE]) score on the Severe Impairment Battery was significantly greater with donepezil 23 mg (+2.6 [0.58]) than with donepezil 10 mg (0.4 [0.66]), p<0.001). Also at week 24, the between-treatment difference in CIBIC-plus score was not significant. In post hoc analysis, least squares mean changes from baseline in SIB score and CIBIC-plus treatment effect at endpoint were greater with donepezil 23 mg than 10 mg in patients with more advanced AD compared with less impaired patients (SIB, +1.6 [0.78] versus -1.5 [0.88], respectively [p<0.001]; CIBIC-plus, 4.31 [1.09] versus 4.42 [1.10] [p=0.028]). Treatment emergent adverse events were reported in 73.3 percent of patients on donepezil 23 mg and 63.7 percent of patients on donepezil 10 mg. The most common adverse effects related the 23 mg dose included nausea (0.9 percent versus 0.2 percent with the 10 mg dose), dizziness (0.7 percent versus 0.2 percent), and vomiting (0.6 versus zero percent). Post hoc analysis of the results of this study was used to gain FDA approval for the marketing of the 23 mg daily donepezil dose.

Dementia Associated with Parkinson's Disease

rivastigmine (Exelon) and placebo

In a 24-week, double-blind study, 541 patients with mild to moderate PD-associated dementia were randomized to receive rivastigmine 1.5 mg twice daily, titrated up to 12 mg daily, or matching placebo.[138] Patients in the rivastigmine group had a mean improvement of 2.1 points (8.8 percent) for the ADAS-cog (a primary efficacy variable) compared to a 0.7 point (2.9 percent) worsening in the placebo group ($p<0.001$). Patients in the rivastigmine group also had more favorable outcomes based on ADSC-CGIC, a primary efficacy measure, with moderate or marked improvement noted in 19.8 percent of patients compared to 14.5 percent of patients in the placebo group ($p=0.02$). Marked or moderate worsening of ADSC-CGIC scores occurred in 33.7 and 42.5 percent of patients in the rivastigmine and placebo groups, respectively. Rivastigmine also provided benefit compared to placebo in ADCS-ADL ($p=0.02$), NPI ($p=0.02$), and MMSE ($p=0.03$). The occurrence of adverse events rated as serious was similar in both groups (13 percent in the rivastigmine group and 14.5 percent in the placebo group, $p=0.69$). However, the predominant adverse events were cholinergic in nature with the most frequent being nausea (affecting 29 percent of patients in the rivastigmine group and 11.2 percent of those in the placebo group, $p<0.001$) and vomiting (affecting 16.6 percent and 1.7 percent, respectively; $p<0.001$). Approximately 17 percent of patients on active treatment prematurely discontinued due to adverse events (compared to eight percent of patients in the placebo group).

META-ANALYSES

Researchers performed a meta-analysis of randomized, double-blind, placebo-controlled, parallel-group trials of donepezil, galantamine, and rivastigmine published through early 2002.[139] They identified 16 trials of over 8,000 patients in which the drugs were used in therapeutic doses for at least 12 weeks and for which a cognitive outcome was reported. The pooled mean proportion of global responders (improvement in CGI-C or CIBIC-plus) to AChEI in excess of that for placebo was ten percent (95% CI, 4-17 percent; $p<0.05$). The number needed to treat (NNT) to yield one additional global responder was 12 (95% CI, 9 to 16). The NNT to yield one additional cognitive responder (four points or greater improvement on ADAS-cog) was 10 (95% CI, 8 to 15). The NNT for one additional patient to experience an adverse event was 12. The rates of adverse events, dropout for any reason, and dropout because of adverse events were all seven to eight percent higher among patients receiving AChEI treatment than among those receiving placebo ($p<0.05$ for all comparisons). The difference among each of the three AChEIs and placebo in adverse events and dropout rates was similar, with the exception of the dropout rate for galantamine (14 percent; 95% CI, 8 to 21 percent) differing from placebo more than that for donepezil (3 percent; 95% CI, 1 to 6 percent).

A meta-analysis using both electronic and manual search strategies examined the effect of donepezil, galantamine, and rivastigmine on AD clinical outcomes and completion rates.[140] Regression analyses compared the effect of dose on clinical outcomes and completion rates, using ten donepezil, six galantamine, and five rivastigmine studies. All three drugs showed beneficial effects on cognitive tests compared to placebo. For donepezil and rivastigmine, larger doses were associated with a larger cognitive effect; this was not the case with galantamine. The odds of clinical global improvement demonstrated superiority over placebo for each drug with no dose effects noted. Dropout rates were greater with galantamine and rivastigmine. There was little difference in dropout rate for each drug at

each dose level except with high-dose donepezil. This was accounted for by the high dropout rate in two 52-week studies using larger doses.

A meta-analysis that included 22 placebo-controlled clinical trials of donepezil, galantamine, and rivastigmine estimated an average 3.9 point reduction in ADAS-cog scores and a 0.26-0.54 point improvement in CIBIC-plus scores from treatment with these agents.[141]

SUMMARY

Alzheimer's disease is an irreversible decline in memory and cognition outside the baseline of normal aging and the most common form of dementia. Medications may assist in delaying the cognitive declines for a period of time in mild to moderate Alzheimer's symptoms. A common pattern of response to treatment with AChEIs is initial improvement in cognition, followed by maintenance of cognitive gains above baseline, but then a final cognitive decline to below baseline levels; however, the final level of cognition in patients receiving pharmacologic treatment remains above the level predicted for those not receiving pharmacologic treatment.

Pharmacologic interventions with the four FDA-approved medications addressed in this review have demonstrated statistically significant improvement over placebo per various scales used to evaluate the changes in patients with dementia due to AD. Most of the scales used to assess outcomes are not practiced routinely in clinical settings, and the interpretation of their clinical significance is dependent on the expertise of the practitioner. In addition, many of the cognitive and functional improvements demonstrated in clinical trials were not clinically important even though they demonstrated statistical significance, so their clinical relevance is unknown. Although the evidence of improvement on global assessment tools was available for donepezil, galantamine, rivastigmine, and memantine, the changes were generally modest and the evidence regarding their effect on quality of life was mixed.

Currently, there is no reliable method established to predict the patients that will have a clinically significant response, and a high percentage of patients diagnosed with AD will unlikely respond to cholinesterase inhibitors. In patients that do respond, these agents provide only modest symptomatic relief, depending on the severity of the disease, for a limited duration of time, and data is lacking to demonstrate efficacy and safety with the long term use of these agents in AD. Reliable evidence is also lacking that proves that the symptomatic treatment with these agents can alter the pathological course of dementia associated with AD or PD. It remains unclear if use of these drugs delays nursing home placement or alters mortality.

The AChEIs are similar per the global and cognitive rating scales, but demonstrate small therapeutic effects at six months. Despite the relatively small treatment effect, the AChEIs are recommended as first-line treatment in patients with mild to moderate AD, primarily due to a lack of effective alternatives. The 2008 ACP and the AAFP dementia practice guidelines do not differentiate among any of the AChEI or memantine (Namenda) when initiating treatment.

Options for the AChEIs vary in terms of formulations and dosing. Galantamine (Razadyne) and rivastigmine (Exelon) are dosed twice daily; whereas, donepezil (Aricept, Aricept ODT), galantamine ER (Razadyne ER) and transdermal rivastigmine (Exelon Patch) are administered once daily. Rivastigmine (Exelon) and galantamine (Razadyne) are available in oral solutions, and donepezil (Aricept ODT) as an orally disintegrating tablet. Rivastigmine (Exelon Patch), which is approved for mild to severe AD as well as mild to moderate PD, is also available as a transdermal patch (for application to the upper or lower back, upper arm or chest), which may improve therapy compliance due to ease of administration

for caregivers. The effectiveness of all the cholinergic products is limited by the maximum tolerated dose.

All of the cholinesterase inhibitors must be slowly titrated upward to minimize the gastrointestinal (GI) adverse effects of the products. Among galantamine, donepezil, and rivastigmine, the incidence of gastrointestinal complaints (nausea, vomiting, diarrhea, anorexia, and weight loss) is the highest with rivastigmine and the lowest with donepezil. Rivastigmine does not have CYP450-mediated drug interactions, which may offer an advantage for some patients on multiple pharmacologic treatments.

The NMDA receptor antagonist, memantine, is approved for the treatment of moderate to severe AD, There are data showing that memantine in combination with AChEIs is beneficial in moderate to severe AD patients.

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